

EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF SODIUM NITRITE

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Outline of Presentation

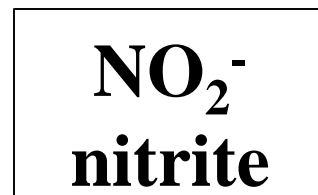
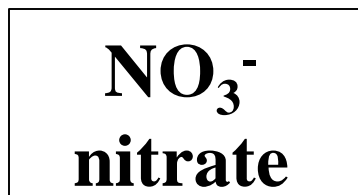
- **Background: chemical properties, metabolism, and exposure**
- **General toxicity**
- **Reproductive toxicity**
- **Developmental toxicity, non-cancer endpoints**
- **Transplacental carcinogenesis**
- **Summary comments**



Sodium nitrite, or nitrous acid sodium salt

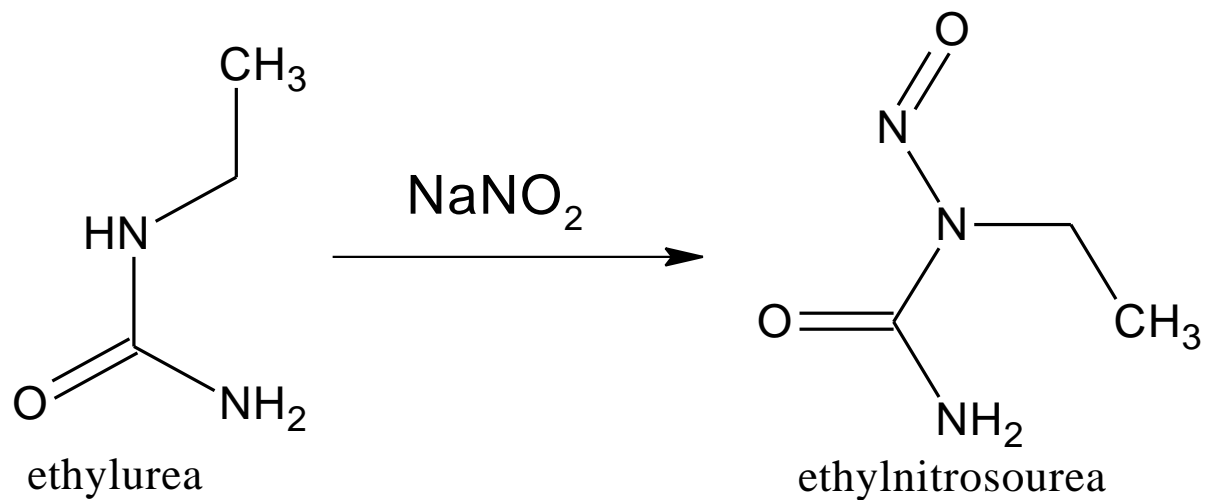
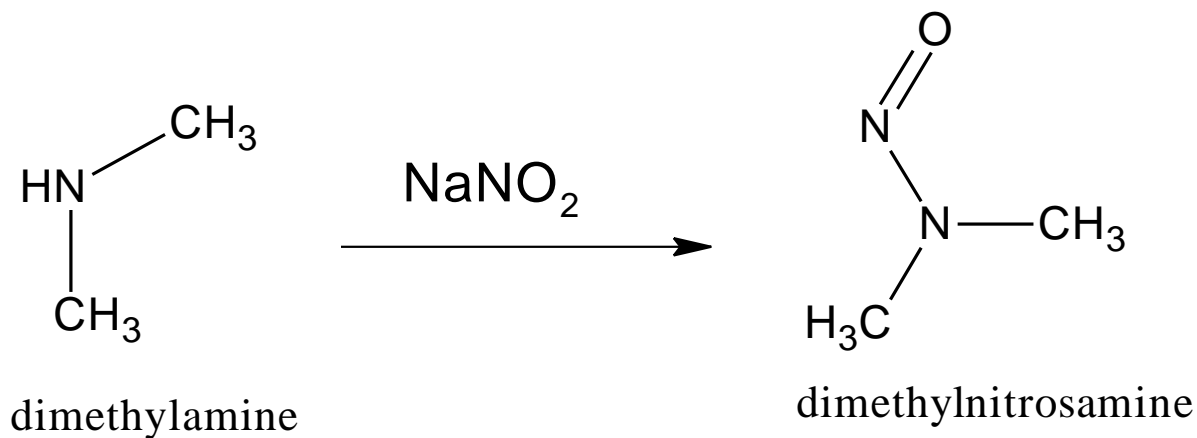
- CAS No. 7632-00-0
- molecular formula: NaNO_2
- molecular weight: 69.00
- water soluble, inorganic salt





- About 5% of an ingested dose of nitrate is reduced to nitrite by microorganisms resident in the oral cavity
- Can also be reduced in the stomach, if pH is sufficiently high

Formation of N-nitroso Compounds



Exposure

Direct exposure to sodium nitrite or nitrite ion, or metabolic conversion from nitrate

- Sodium nitrite added to cured meats as a preservative, color fixative, and flavor enhancer
- Nitrite and nitrate naturally present in vegetables
- Nitrite and nitrate can be present in drinking water



Methemoglobin (MetHb)

- Nitrite in the blood participates in an oxidation reaction with hemoglobin (Hb) to form MetHb
- MetHb cannot carry oxygen
- Ascorbic acid (and other antioxidants) may slow the rate of MetHb formation
- Reduction of MetHb to Hb is catalyzed by NADPH-MetHb-reductase
- Methylene blue is used therapeutically to accelerate MetHb-reductase activity



Effects on Fertility

- **No human data**
- **Six pair-based animal studies of sodium nitrite, and one of potassium nitrite**
 - NTP continuous breeding study in mice
 - One-generation feeding study in rats
 - One-generation study of rats fed sodium nitrite-treated meat
 - Three-generation drinking water study in rats
 - One-generation drinking water study in mice
 - Subchronic study of rats fed sodium nitrite-treated fish
 - Drinking water study of potassium nitrite in guinea pigs
- **No effects observed on parameters of fertility**



Effects on Other Reproductive Parameters

- **Female Reproductive Toxicity**

- Five studies reported on non-fertility reproductive endpoints in females
- One report of reduced offspring growth suggested a possible lactation-suppressing effect in mice
- Inflamed reproductive organs and placental degeneration in guinea pigs given potassium nitrite during pregnancy

- **Male Reproductive Toxicity**

- Five studies reported on non-fertility reproductive endpoints in males
- Two studies reported on testicular changes in rats, which could not be conclusively attributed to sodium nitrite exposure



New Data Relevant to Reproductive Toxicity (NTP Draft Technical Report; Peer Review Date, 18 May 2000)

- **14- week drinking water studies in male and female rats and mice**
 - Significantly reduced sperm motility in both species at higher concentrations; apparent concentration response
 - Testicular degeneration in mice at the two highest concentrations
 - Estrous cycle length significantly increased at higher concentrations in mice
 - Survival not affected; reduced body weights and increased relative weights for some organs at the highest concentrations
 - Rats showed more clinical symptoms of methemoglobinemia than did mice; no NOAEL for increased methemoglobin in rats
- **2-year drinking water studies in male and female rats and mice**
 - No notable histopathological changes in the reproductive organs of male or female rats or mice
 - Survival not affected; reduced body weights at highest concentration



Effects on Development – Human Data

- **No data available on sodium nitrite**
- **Case-control studies of two populations exposed to nitrate in drinking water during pregnancy**
 - Australia: significant increased risk for CNS malformations, also for all malformations with an apparent dose effect
 - Canada: non-significant increased risk for CNS malformations
- **Study of pregnant women given nitrosatable drugs**
 - Can undergo nitrosation to form N-nitroso compounds
 - Significantly increased risk for major malformations with exposure during first four months of pregnancy



Effects on Development in Guinea Pigs

- **Sodium nitrite (s.c.)**
 - Two studies; several small experiments
 - Ascorbic acid deficient vs non-deficient animals
 - Increased abortion in treated/deficient animals at lower doses than in treated/non-deficient animals
 - Prevented by methylene blue
 - Fetal deaths associated with increased maternal MetHb
- **Potassium nitrite (drinking water)**
 - One study; small groups of guinea pigs
 - Males and females exposed
 - One maternal death, reduced weight gain at high dose
 - All fetuses died at two highest doses
 - Increased fetal loss in all treated litters, no statistics



Effects on Development in Mice

- **Study of erythropoiesis on gestation days 14, 16, and 18**
 - Treatment of dams by gavage, throughout gestation
 - Maternal effects not reported
 - No effects on viability or gross morphology
 - Significant changes in parameters of hepatic erythropoiesis
- **Developmental toxicity study**
 - Treatment of dams by gavage, gestation days 6-15
 - Minimal maternal toxicity at highest doses
 - Apparent decrease in viability probably not related to treatment
- **Drinking water study**
 - Treatment of dams via drinking water, gestation days 7-18
 - No significant effects on dams or fetuses



Effects on Development in Rats

- **Three studies of neurobehavioral parameters**
 - Treated drinking water to dams from gestation day 13
 - Some animals given nimodipine (neuroprotective, antihypoxic)
 - Impairments of discrimination learning and long-term retention of passive avoidance
 - Effects on open field activity
 - Hyperreactivity to footshock, and prolonged stress response
 - Effects on ingrowth of nerve fibers
 - Effects prevented or alleviated by nimodipine
- **One drinking water study; exposure throughout gestation and lactation**
 - Maternal effects not reported
 - Birthweights similar among groups
 - Mean litter size lower in treated animals; no statistics



Placental Transport

- **Nitrite found in fetal blood following maternal dosing (oral or injection) of rats and guinea pigs**
- **Nitrite shown to cross the placenta in dairy cows**
- **Nitrite dosing of pregnant animals resulted in elevated methemoglobin in fetuses as well as mothers**



Toxicosis

- **Methemoglobinemia in pregnant and lactating animals**
 - Pregnant rats more sensitive to acute lethality
 - Chronically exposed pregnant rats became severely anemic, while non-pregnant rats maintained control Hb levels
 - *In vitro*, erythrocytes from pregnant mice had higher velocity of MetHb formation
- **Maternal and fetal toxicosis in infused dairy cows**
 - Maternal effects: increased MetHb, reduced blood pressure, increased heart rate, and decreased arterial PO₂
 - Nitrite appeared in fetal circulation, and fetal MetHb levels rose
 - Fetal heart rates were affected, and fetal PO₂ depressed
 - No increase in frequency of premature delivery or abortion



Available Evidence

- **Reproductive toxicity**
 - No human data
 - Fertility in animals
 - Other reproductive endpoints in animals
- **Developmental toxicity (non-cancer endpoints)**
 - Human data on nitrates and nitrosatable drugs
 - Animal data from three species
 - Studies on placental transport, methemoglobinemia during pregnancy, and nitrite toxicosis in pregnant animals
- **Transplacental carcinogenicity**
 - Animal models
 - Human data on nitrite-containing foods

